

previously disclosed to the public, as such disclosure is defined in § 20.81, or they relate to a device for which a PMA has been abandoned and they no longer represent a trade secret or confidential commercial or financial information as defined in § 20.61:

(1) Manufacturing methods or processes, including quality control procedures.

(2) Production, sales, distribution, and similar data and information, except that any compilation of such data and information aggregated and prepared in a way that does not reveal data or information which are not available for public disclosure under this provision is available for public disclosure.

(3) Quantitative or semiquantitative formulas.

[51 FR 26364, July 22, 1986, as amended at 61 FR 51531, Oct. 2, 1996]

§ 814.15 Research conducted outside the United States.

(a) A study conducted outside the United States submitted in support of a PMA and conducted under an IDE shall comply with part 812. A study conducted outside the United States submitted in support of a PMA and not conducted under an IDE shall comply with the provisions in paragraph (b) or (c) of this section, as applicable.

(b) *Research begun on or after effective date.* FDA will accept studies submitted in support of a PMA which have been conducted outside the United States and begun on or after November 19, 1986, if the data are valid and the investigator has conducted the studies in conformance with the "Declaration of Helsinki" or the laws and regulations of the country in which the research is conducted, whichever accords greater protection to the human subjects. If the standards of the country are used, the applicant shall state in detail any differences between those standards and the "Declaration of Helsinki" and explain why they offer greater protection to the human subjects.

(c) Research begun before effective date. FDA will accept studies submitted in support of a PMA which have been conducted outside the United States and begun before November 19, 1986, if FDA is satisfied that the data

are scientifically valid and that the rights, safety, and welfare of human subjects have not been violated.

(d) *As sole basis for marketing approval.* A PMA based solely on foreign clinical data and otherwise meeting the criteria for approval under this part may be approved if:

(1) The foreign data are applicable to the U.S. population and U.S. medical practice;

(2) The studies have been performed by clinical investigators of recognized competence; and

(3) The data may be considered valid without the need for an on-site inspection by FDA or, if FDA considers such an inspection to be necessary, FDA can validate the data through an on-site inspection or other appropriate means.

(e) *Consultation between FDA and applicants.* Applicants are encouraged to meet with FDA officials in a "pre-submission" meeting when approval based solely on foreign data will be sought.

(Approved by the Office of Management and Budget under control number 0910-0231)

[51 FR 26364, July 22, 1986; 51 FR 40415, Nov. 7, 1986, as amended at 51 FR 43344, Dec. 2, 1986]

§ 814.17 Service of orders.

Orders issued under this part will be served in person by a designated officer or employee of FDA on, or by registered mail to, the applicant or the designated agent at the applicant's or designated agent's last known address in FDA's records.

§ 814.19 Product development protocol (PDP).

A class III device for which a product development protocol has been declared completed by FDA under this chapter will be considered to have an approved PMA.

Subpart B—Premarket Approval Application (PMA)

§ 814.20 Application.

(a) The applicant or an authorized representative shall sign the PMA. If the applicant does not reside or have a place of business within the United States, the PMA shall be countersigned

by an authorized representative residing or maintaining a place of business in the United States and shall identify the representative's name and address.

(b) Unless the applicant justifies an omission in accordance with paragraph (d) of this section, a PMA shall include:

(1) The name and address of the applicant.

(2) A table of contents that specifies the volume and page number for each item referred to in the table. A PMA shall include separate sections on non-clinical laboratory studies and on clinical investigations involving human subjects. A PMA shall be submitted in six copies each bound in one or more numbered volumes of reasonable size. The applicant shall include information that it believes to be trade secret or confidential commercial or financial information in all copies of the PMA and identify in at least one copy the information that it believes to be trade secret or confidential commercial or financial information.

(3) A summary in sufficient detail that the reader may gain a general understanding of the data and information in the application. The summary shall contain the following information:

(i) *Indications for use.* A general description of the disease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended.

(ii) *Device description.* An explanation of how the device functions, the basic scientific concepts that form the basis for the device, and the significant physical and performance characteristics of the device. A brief description of the manufacturing process should be included if it will significantly enhance the reader's understanding of the device. The generic name of the device as well as any proprietary name or trade name should be included.

(iii) *Alternative practices and procedures.* A description of existing alternative practices or procedures for diagnosing, treating, preventing, curing, or mitigating the disease or condition for which the device is intended.

(iv) *Marketing history.* A brief description of the foreign and U.S. marketing history, if any, of the device, including

a list of all countries in which the device has been marketed and a list of all countries in which the device has been withdrawn from marketing for any reason related to the safety or effectiveness of the device. The description shall include the history of the marketing of the device by the applicant and, if known, the history of the marketing of the device by any other person.

(v) *Summary of studies.* An abstract of any information or report described in the PMA under paragraph (b)(8)(ii) of this section and a summary of the results of technical data submitted under paragraph (b)(6) of this section. Such summary shall include a description of the objective of the study, a description of the experimental design of the study, a brief description of how the data were collected and analyzed, and a brief description of the results, whether positive, negative, or inconclusive. This section shall include the following:

(A) A summary of the nonclinical laboratory studies submitted in the application;

(B) A summary of the clinical investigations involving human subjects submitted in the application including a discussion of subject selection and exclusion criteria, study population, study period, safety and effectiveness data, adverse reactions and complications, patient discontinuation, patient complaints, device failures and replacements, results of statistical analyses of the clinical investigations, contraindications and precautions for use of the device, and other information from the clinical investigations as appropriate (any investigation conducted under an IDE shall be identified as such).

(vi) *Conclusions drawn from the studies.* A discussion demonstrating that the data and information in the application constitute valid scientific evidence within the meaning of § 860.7 and provide reasonable assurance that the device is safe and effective for its intended use. A concluding discussion shall present benefit and risk considerations related to the device including a discussion of any adverse effects of the

device on health and any proposed additional studies or surveillance the applicant intends to conduct following approval of the PMA.

(4) A complete description of:

(i) The device, including pictorial representations;

(ii) Each of the functional components or ingredients of the device if the device consists of more than one physical component or ingredient;

(iii) The properties of the device relevant to the diagnosis, treatment, prevention, cure, or mitigation of a disease or condition;

(iv) The principles of operation of the device; and

(v) The methods used in, and the facilities and controls used for, the manufacture, processing, packing, storage, and, where appropriate, installation of the device, in sufficient detail so that a person generally familiar with current good manufacturing practice can make a knowledgeable judgment about the quality control used in the manufacture of the device.

(5) Reference to any performance standard under section 514 of the act or under section 534 of Subchapter C—Electronic Product Radiation Control of the Federal Food, Drug, and Cosmetic Act (formerly the Radiation Control for Health and Safety Act of 1968) in effect or proposed at the time of the submission and to any voluntary standard that is relevant to any aspect of the safety or effectiveness of the device and that is known to or that should reasonably be known to the applicant. The applicant shall—

(i) Provide adequate information to demonstrate how the device meets, or justify any deviation from, any performance standard established under section 514 of the act or under section 534 of Subchapter C—Electronic Product Radiation Control of the Federal Food, Drug, and Cosmetic Act (formerly the Radiation Control for Health and Safety Act of 1968), and

(ii) Explain any deviation from a voluntary standard.

(6) The following technical sections which shall contain data and information in sufficient detail to permit FDA to determine whether to approve or deny approval of the application:

(i) A section containing results of the nonclinical laboratory studies with the device including microbiological, toxicological, immunological, biocompatibility, stress, wear, shelf life, and other laboratory or animal tests as appropriate. Information on nonclinical laboratory studies shall include a statement that each such study was conducted in compliance with part 58, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

(ii) A section containing results of the clinical investigations involving human subjects with the device including clinical protocols, number of investigators and subjects per investigator, subject selection and exclusion criteria, study population, study period, safety and effectiveness data, adverse reactions and complications, patient discontinuation, patient complaints, device failures and replacements, tabulations of data from all individual subject report forms and copies of such forms for each subject who died during a clinical investigation or who did not complete the investigation, results of statistical analyses of the clinical investigations, device failures and replacements, contraindications and precautions for use of the device, and any other appropriate information from the clinical investigations. Any investigation conducted under an IDE shall be identified as such. Information on clinical investigations involving human subjects shall include the following:

(A) A statement with respect to each study that it either was conducted in compliance with the institutional review board regulations in part 56, or was not subject to the regulations under § 56.104 or § 56.105, and that it was conducted in compliance with the informed consent regulations in part 50; or if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance.

(B) A statement that each study was conducted in compliance with part 812

or part 813 concerning sponsors of clinical investigations and clinical investigators, or if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance.

(7) For a PMA supported solely by data from one investigation, a justification showing that data and other information from a single investigator are sufficient to demonstrate the safety and effectiveness of the device and to ensure reproducibility of test results.

(8)(i) A bibliography of all published reports not submitted under paragraph (b)(6) of this section, whether adverse or supportive, known to or that should reasonably be known to the applicant and that concern the safety or effectiveness of the device.

(ii) An identification, discussion, and analysis of any other data, information, or report relevant to an evaluation of the safety and effectiveness of the device known to or that should reasonably be known to the applicant from any source, foreign or domestic, including information derived from investigations other than those proposed in the application and from commercial marketing experience.

(iii) Copies of such published reports or unpublished information in the possession of or reasonably obtainable by the applicant if an FDA advisory committee or FDA requests.

(9) One or more samples of the device and its components, if requested by FDA. If it is impractical to submit a requested sample of the device, the applicant shall name the location at which FDA may examine and test one or more devices.

(10) Copies of all proposed labeling for the device. Such labeling may include, e.g., instructions for installation and any information, literature, or advertising that constitutes labeling under section 201(m) of the act.

(11) An environmental assessment under § 25.20(n) prepared in the applicable format in § 25.40, unless the action qualifies for exclusion under § 25.30 or § 25.34. If the applicant believes that the action qualifies for exclusion, the PMA shall under § 25.15(a) and (d) provide information that establishes to FDA's satisfaction that the action re-

quested is included within the excluded category and meets the criteria for the applicable exclusion.

(12) A financial certification or disclosure statement or both as required by part 54 of this chapter.

(13) Such other information as FDA may request. If necessary, FDA will obtain the concurrence of the appropriate FDA advisory committee before requesting additional information.

(c) Pertinent information in FDA files specifically referred to by an applicant may be incorporated into a PMA by reference. Information in a master file or other information submitted to FDA by a person other than the applicant will not be considered part of a PMA unless such reference is authorized in writing by the person who submitted the information or the master file. If a master file is not referenced within 5 years after the date that it is submitted to FDA, FDA will return the master file to the person who submitted it.

(d) If the applicant believes that certain information required under paragraph (b) of this section to be in a PMA is not applicable to the device that is the subject of the PMA, and omits any such information from its PMA, the applicant shall submit a statement that identifies the omitted information and justifies the omission. The statement shall be submitted as a separate section in the PMA and identified in the table of contents. If the justification for the omission is not accepted by the agency, FDA will so notify the applicant.

(e) The applicant shall periodically update its pending application with new safety and effectiveness information learned about the device from ongoing or completed studies that may reasonably affect an evaluation of the safety or effectiveness of the device or that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling. The update report shall be consistent with the data reporting provisions of the protocol. The applicant shall submit three copies of any update report and shall include in the report the number assigned by FDA to the PMA. These updates are considered to be amendments to the PMA.

The time frame for review of a PMA will not be extended due to the submission of an update report unless the update is a major amendment under § 814.37(c)(1). The applicant shall submit these reports—

- (1) 3 months after the filing date,
- (2) Following receipt of an approvable letter, and
- (3) At any other time as requested by FDA.

(f) If a color additive subject to section 721 of the act is used in or on the device and has not previously been listed for such use, then, in lieu of submitting a color additive petition under part 71, at the option of the applicant, the information required to be submitted under part 71 may be submitted as part of the PMA. When submitted as part of the PMA, the information shall be submitted in three copies each bound in one or more numbered volumes of reasonable size. A PMA for a device that contains a color additive that is subject to section 721 of the act will not be approved until the color additive is listed for use in or on the device.

(g) Additional information on FDA policies and procedures, as well as links to PMA guidance documents, is available on the Internet at <http://www.fda.gov/cdrh/devadvice/pma/>.

(h) If you are sending a PMA, PMA amendment, PMA supplement, or correspondence with respect to a PMA, you must send the submission to the appropriate address as follows:

(1) For devices regulated by the Center for Devices and Radiological Health, send it to: Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850.

(2) For devices regulated by the Center for Biologics Evaluation and Research, send it to: Document Control Center (HFM-99), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852-1448.

(3) For devices regulated by the Center for Drug Evaluation and Research, send it to: Central Document Control Room, Center for Drug Evaluation and Research, Food and Drug Administra-

tion, 5901-B Ammendale Rd., Beltsville, MD 20705-1266.

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§ 814.37 PMA amendments and resubmitted PMA's.

(a) An applicant may amend a pending PMA or PMA supplement to revise existing information or provide additional information.

(b) FDA may request the applicant to amend a PMA or PMA supplement with any information regarding the device that is necessary for FDA or the appropriate advisory committee to complete the review of the PMA or PMA supplement.

(c) A PMA amendment submitted to FDA shall include the PMA or PMA supplement number assigned to the original submission and, if submitted on the applicant's own initiative, the reason for submitting the amendment. FDA may extend the time required for its review of the PMA, or PMA supplement, as follows:

(1) If the applicant on its own initiative or at FDA's request submits a major PMA amendment (e.g., an amendment that contains significant new data from a previously unreported study, significant updated data from a previously reported study, detailed new analyses of previously submitted data, or significant required information previously omitted), the review period may be extended up to 180 days.

(2) If an applicant declines to submit a major amendment requested by FDA, the review period may be extended for the number of days that elapse between the date of such request and the date that FDA receives the written response declining to submit the requested amendment.

(d) An applicant may on its own initiative withdraw a PMA or PMA supplement. If FDA requests an applicant to submit a PMA amendment and a written response to FDA's request is not received within 180 days of the date of the request, FDA will consider the pending PMA or PMA supplement to be